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Rates of hypoglycaemia are lower in patients treated with insulin degludec/liraglutide (IDegLira) than with IDeg or insulin glargine regardless of the hypoglycaemia definition used

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Running title: Hypoglycaemia rates for IDegLira vs. IDeg, IGlar U100 and liraglutide

Abstract

Aims: The rates of hypoglycaemia reported in clinical trials are affected by the definitions of hypoglycaemia used. This *post-hoc* analysis took data from two trials comparing the once-daily, fixed ratio combination of insulin degludec/liraglutide (IDegLira) with basal insulin regimens, and re-analysed these data using alternative hypoglycaemia definitions and stratified outcomes by dosing time and baseline characteristics.

Materials and methods: *Post hoc* analyses of the DUAL I (patients uncontrolled on oral antidiabetic drugs) and DUAL V (patients uncontrolled on insulin glargine (IGlar) U100) trials were carried out using different definitions of hypoglycaemia and by whether treatments were administered in the AM or PM. Rates of hypoglycaemia for the definitions of confirmed and ADA-documented symptomatic hypoglycaemia were compared according to age, gender and BMI.

Results: Although hypoglycaemia rates differed with the alternative hypoglycaemia definitions, rates were consistently lower with IDegLira versus IDeg and IGlar U100. Despite HbA_{1c} being lower with IDegLira at end of treatment, confirmed and nocturnal-confirmed hypoglycaemia rates were lower

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for IDegLira versus IDeg and IGlar U100, irrespective of dosing time. The definitions of confirmed and ADA documented symptomatic hypoglycaemia did not have a significant effect on the treatment difference between IDegLira and IDeg, liraglutide or IGlar U100 when further assessed by baseline age, gender and BMI.

Conclusions: Treatment with IDegLira, versus IDeg and IGlar U100, resulted in lower rates of hypoglycaemia regardless of dosing time and definition of hypoglycaemia used. The choice of hypoglycaemia definition did not influence the results of analyses when stratified by age, sex and BMI.

Introduction

Insulin degludec/liraglutide (IDegLira) is a once-daily combination of insulin degludec (IDeg), a basal insulin with a long duration of action,[1] and the glucagon-like peptide-1 receptor agonist (GLP-1 RA), liraglutide. In clinical trials, IDegLira has been associated with lower rates of hypoglycaemia versus the basal insulin comparators of IDeg (in the DUAL I clinical trial, NCT01336023[2]) and insulin glargine (IGlar) U100 (in the DUAL V clinical trial, NCT01952145[3]), despite achieving significantly better glycaemic control.

The purpose of the current study was to re-analyse, using a series of alternative hypoglycaemia definitions, data from two trials, DUAL I and V, in which IDegLira was compared with basal insulin therapy. In the DUAL I and DUAL V trials, the original definition of confirmed hypoglycaemia used was plasma glucose (PG) <3.1 mmol/L (<56 mg/dL) or patient unable to self-treat, and an episode was classified as nocturnal hypoglycaemia if occurring between 00:01 and 05:59 (both inclusive). Several other definitions of hypoglycaemia are described in the literature, however, and have been used across different diabetes clinical trials,[4] and the rates of hypoglycaemia reported in a clinical trial will inevitably be affected by the definitions used.[5] Recently the International Hypoglycaemia Study Group released a joint ADA/EASD statement stating that a single glucose level should be agreed to, which would allow efficacy of intervention comparisons to be made with greater statistical power.[6] It is also possible that any differences in outcomes associated with differing dosing times, for example the rate of nocturnal hypoglycaemia, could be masked by the overall hypoglycaemia advantages reported for IDegLira in these studies. Therefore, the hypoglycaemia results were also analysed by dosing time, and by varying the definition of the nocturnal period to better characterise the clinical profile of IDegLira with regard to its relative risks for hypoglycaemia. In addition, previous analyses have shown that IDegLira is efficacious regardless of baseline characteristics, such as BMI[7] and HbA_{1c}.[8] This analysis therefore assessed whether the relative risk of hypoglycaemia was influenced by key baseline characteristics, again using the different definitions.

Material and Methods

The DUAL I clinical trial compared the efficacy and safety of IDegLira to its individual components, in insulin-naïve patients with type 2 diabetes previously uncontrolled on metformin +/- pioglitazone. Patients were randomized 2:1:1 to receive IDegLira (N=834), IDeg (N=414) or liraglutide (N=415) over the 26-week main trial period;[2] 1311 patients continued treatment into the 26-week extension period (ext); N=665, 333 and 313 for IDegLira, IDeg and liraglutide, respectively.[7] IDegLira treatment was initiated at 10 dose steps daily (10 units of IDeg plus 0.36 mg of liraglutide); similarly, IDeg treatment was initiated at 10 units daily. Liraglutide treatment was initiated at a daily dose of 0.6 mg, increased by 0.6 mg each week until a final dose of 1.8 mg/day was reached. IDegLira and IDeg were titrated twice-weekly to a fasting plasma glucose target of 4–5 mmol/L (72–90 mg/dL), with a maximum dose of 50 dose steps for IDegLira, but no maximum dose for IDeg.[7]

In the DUAL V trial, IDegLira was compared with continued up-titration of IGlar U100 in patients with type 2 diabetes previously uncontrolled on IGlar U100 (20–50 units daily) and metformin.[3] There were 557 patients randomized 1:1 to receive IDegLira or IGlar U100 (N=278 and 279, respectively) over a 26-week period. IDegLira was initiated at 16 dose steps (16 units of IDeg plus 0.58 mg of liraglutide) administered once-daily at any time of day, although preferably at the same time of day throughout the trial. Meanwhile IGlar U100 was continued at pre-trial daily dose and administered once-daily according to local prescribing instructions. Similarly to DUAL I, IDegLira and IGlar U100 were titrated twice-weekly to a fasting plasma glucose target of 4–5 mmol/L with a maximum dose of 50 dose steps for IDegLira, but no maximum dose for IGlar U100.[3]

Post hoc analyses of the DUAL I/ext and DUAL V trial data were carried out according to different definitions of hypoglycaemia (Table 1) and according to whether both treatments were administered in the AM (00:00–11:59 h) or the PM (12:00–23:59 h). In addition, the rates of hypoglycaemia for the definitions of confirmed hypoglycaemia and ADA documented symptomatic hypoglycaemia were compared with patient data stratified according to the baseline characteristics of age (<65 and ≥65

years), gender and body mass index (BMI) (<25, ≥25–<30, ≥30–<35 and ≥35 kg/m^2). The proportions of patients achieving an HbA_{1c} of either less than 7% or less than or equal to 6.5%, the proportions achieving these targets with no confirmed hypoglycaemia, and those achieving these targets with no confirmed hypoglycaemia and no weight gain, has been described previously for DUAL I[2] and DUAL V;[3] hypoglycaemia was defined in these reports as the patient unable to self-treat or plasma glucose <3.1 mmol/L (<56 mg/dL). The current *post-hoc* analysis examined the same endpoints using the ADA documented symptomatic hypoglycaemia definition (Table 1). Protocols were approved by institutional review boards and studies were done in accordance with the Declaration of Helsinki.

Statistical methods

The number of hypoglycaemic events according to the definition of hypoglycaemia, dosing time and baseline characteristics was analysed based on the full analysis set using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, country/region and relevant stratification factors (in DUAL I/ext only) of previous OAD treatment, baseline HbA_{1c} stratum; and substudy participation as fixed effects. Analyses of hypoglycaemia according to baseline characteristics further included the baseline group and an interaction term between baseline group and treatment as fixed effects in the model. For the proportion of patients achieving HbA_{1c} targets, odds ratios were estimated from a logistic regression model with treatment, region, and relevant stratification factors as fixed factors and baseline HbA_{1c} and weight, when weight was included in the composite, as covariates.

Results

Hypoglycaemia rates according to different definitions

Regardless of the hypoglycaemia definition used, rates of hypoglycaemia were lower in patients treated with IDegLira than with IDeg, for both DUAL I and DUAL I ext, or with IGlar U100 in DUAL V, but higher than in patients treated with liraglutide, for both DUAL I and DUAL I ext (Table 2). The lower hypoglycaemia rates in comparison with basal insulin therapy with IDeg or IGlar U100 were achieved despite significantly greater end of trial HbA_{1c} reductions with IDegLira therapy.[2,3,7]

Hypoglycaemia estimated rate ratios by treatment were statistically significantly lower for patients treated with IDegLira compared with IDeg or IGlar U100 for all definitions of overall hypoglycaemia, including confirmed symptomatic and ADA-documented symptomatic episodes (DUAL I ext and DUAL V shown in Figure 1, DUAL I shown in Supplementary Figure 1). Very few of the total hypoglycaemia events were categorized as severe (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions); in DUAL I there were three severe events with IDegLira, two with IDeg and none with liraglutide, in DUAL I ext, at the end of 52 weeks there were three severe events with IDegLira (those reported in the main DUAL I trial), two with IDeg (those reported in the main DUAL I trial) and two with liraglutide,[7] and in DUAL V one severe event with IGlar U100 and none with IDegLira.[3] For nocturnal hypoglycaemia, rates were statistically significantly lower in patients treated with IDegLira than with IDeg for both DUAL I and DUAL I ext for the definition of nocturnal confirmed hypoglycaemia (unable to self-treat or <3.1 mmol/L [<56 mg/dL], 00:01–7:59 h). For the nocturnal ADA-documented symptomatic hypoglycaemia definition, the rate was significantly lower with IDegLira in DUAL I ext (Figure 1A). Liraglutide treatment, in comparison with IDegLira, resulted in statistically significantly lower rates of hypoglycaemia in DUAL I and DUAL I ext for all definitions except nocturnal confirmed symptomatic hypoglycaemia, where statistical analyses could not be carried out due to the low number of events in the liraglutide arm.

The cumulative mean number of ADA-documented symptomatic episodes per patient for IDegLira, IDeg and liraglutide from DUAL I and DUAL I ext are shown in Figure 2A, and for IDegLira and IGlar U100 from DUAL V, in Figure 2B. The equivalent data for nocturnal ADA-documented symptomatic hypoglycaemia are given in Supplementary Figure 2. For comparison, the cumulative mean number of overall and nocturnal events per patient, by treatment, using the original confirmed hypoglycaemia definition can be seen in Supplementary Figure 3.

Hypoglycaemia rates by dosing time

Confirmed hypoglycaemia rates for IDegLira, IDeg and liraglutide when all treatments were dosed in the AM were 1.68, 2.76 and 0.22 events per patient-year of exposure (PYE), respectively, in DUAL I and 1.66, 3.11 and 0.18 events per PYE in DUAL I ext. When all treatments were dosed in the PM, confirmed hypoglycaemia rates for IDegLira, IDeg and liraglutide, respectively were 1.94, 2.42 and 0.22 events per PYE in DUAL I, and 1.89, 2.53 and 0.20 events per PYE in DUAL I ext. Nocturnal confirmed hypoglycaemia rates for IDegLira, IDeg and liraglutide, respectively, when all treatments were dosed in the AM were 0.22, 0.29 and 0.01 events per PYE in DUAL I, and 0.22, 0.48 and 0.01 events per PYE in DUAL I ext. When all treatments were dosed in the PM, the respective confirmed nocturnal hypoglycaemia rates were 0.23, 0.27 and 0.05 events per PYE in DUAL I, and 0.23, 0.27 and 0.03 events per PYE in DUAL I ext. The estimated rate ratios for DUAL I and DUAL I ext show that; in patients treated with IDegLira, confirmed hypoglycaemia rates were statistically significantly lower than with IDeg for AM dosing of both treatments; for PM dosing of both treatments DUAL I ext showed a statistically significant difference between IDegLira and IDeg treatment (Figure 3A). Nocturnal confirmed hypoglycaemia rates were lower in patients treated with IDegLira than with IDeg, but the difference was only statistically significant for AM dosing of both treatments in DUAL I ext. For PM dosing, there was no statistically significant difference between treatment with IDegLira and IDeg in DUAL I or DUAL I ext for nocturnal hypoglycaemia (Figure 3A). Compared with IDegLira,

treatment with liraglutide resulted in statistically significantly lower rates of confirmed and nocturnal confirmed hypoglycaemia, whether both treatments were dosed in the AM or PM, for both DUAL I and DUAL I ext (Figure 2B). Confirmed hypoglycaemia rates for IDegLira and IGlar U100 were 2.18 and 6.86 events per PYE, respectively, when dosed in the AM and 2.26 and 4.59 events per PYE when dosed in the PM. Nocturnal confirmed hypoglycaemia rates were 0.22 and 1.67 events per PYE, for IDegLira and IGlar U100 respectively, when both treatments were dosed in the AM and 0.23 and 1.12 events per PYE when dosed in the PM. IDegLira treatment resulted in statistically significantly lower rates of confirmed and nocturnal confirmed hypoglycaemia than IGlar U100, whether both treatments were dosed in the AM or PM (Figure 3C).

Confirmed and ADA-documented symptomatic hypoglycaemia rates by baseline characteristics

The analyses of confirmed hypoglycaemia and ADA-documented symptomatic hypoglycaemia definitions, according to baseline characteristics of age, gender and BMI showed generally consistent rates for both hypoglycaemia definitions for DUAL I (Supplementary Table 1A) and DUAL V (Supplementary Table 1B) between the treatment groups. Interaction analyses showed there was no statistically significant effect of age, gender or BMI on the estimated treatment rate ratio for IDegLira versus IDeg for both confirmed and ADA-documented symptomatic hypoglycaemia (all p >0.10). Comparing IDegLira with liraglutide, there was no statistically significant effect of age, gender or BMI on the estimated treatment rate ratio for confirmed hypoglycaemia (p=0.2565, p=0.2635 and p=0.2372, respectively), but while gender and BMI had no significant effect on ADA-documented symptomatic hypoglycaemia rate ratio (p=0.2090 and p=0.0659 , respectively), there was a significant difference seen between <65 years and $\geq$65 years (p=0.025), with the rate ratio (favouring liraglutide) being relatively much greater for patients aged >65 years using this definition.

Proportion of patients achieving combined end points

The proportions of patients achieving an HbA_{1c} less than 7%, or of 6.5% or less, those achieving the HbA_{1c} targets with no ADA-documented symptomatic hypoglycaemia, and those achieving these targets with no ADA-documented symptomatic hypoglycaemia and no weight gain are given in Supplementary Table 2. The odds of achieving an HbA_{1c} less than 7% or of 6.5% or less without ADA-documented symptomatic hypoglycaemia and without ADA-documented symptomatic hypoglycaemia and weight gain were statistically significantly greater with IDegLira than with IDeg and IGlar U100 (p<0.0001 for all comparisons). A greater proportion of patients reached these targets with liraglutide than with IDegLira, and this difference in odds was statistically significant for HbA_{1c} less than 7% with no ADA documented symptomatic hypoglycaemia or weight gain (p<0.0001), HbA_{1c} of 6.5% or less with no ADA-documented symptomatic hypoglycaemia (p=0.0006) and HbA_{1c} of 6.5% or less with no ADA-documented symptomatic hypoglycaemia or weight gain (p=0.0061). It was not significantly different for HbA_{1c} less than 7% with no ADA-documented symptomatic hypoglycaemia (p=0.9075).

Discussion

IDegLira treatment has previously been shown to result in greater improvements in glycaemic control than IDeg[2,7] or IGlar U100[3] and despite the greater HbA_{1c} reduction, hypoglycaemia rates were lower. The present *post-hoc* analyses extend this finding to show that confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia rates were lower for IDegLira in comparison with IDeg and IGlar U100 irrespective of dosing time, and regardless of the hypoglycaemia definitions used. One explanation for the lower rates of hypoglycaemia is the glucose-dependant mode of action of GLP-1 RAs concomitant to the insulin sparing effect when GLP-1RA is used together with insulin. One of the findings of our analysis was that the advantage of IDegLira with regard to nocturnal hypoglycaemia was unaffected by the definition of the nocturnal period. It is

possible that the insulin degludec component of IDegLira becomes a relatively more critical determinant of risk in the nocturnal period as IDeg is associated with low variability in the glucose-lowering effect across 24 hours and from day to day.[10] Importantly, a similar finding was made in a meta-analysis of data from trials comparing IDeg with IGlar U100.[11] Here, the number of episodes per PYE were again similar across different definitions of nocturnal hypoglycaemia, and the advantage of IDeg was preserved.[11]

The definition of ADA-documented symptomatic hypoglycaemia resulted in greater numbers of episodes per PYE than the original definition and this is primarily due to the raised glycaemic threshold at which hypoglycaemia is recognised in the ADA definition (≤3.9 mmol/L [≤70 mg/dL] as opposed to <3.1 mmol/L [<56 mg/dL]) combined with the low titration target applied in the trials (4.0–5.0 mmol/L). Higher event rates were also produced by changing the definition of the nocturnal period to 00:01–07:59 h, possibly due to this including the pre-breakfast self-monitored plasma glucose (SMPG) measurement and/or the influence of diabetes therapies within this interval when taken at an early breakfast. The profiles for IDegLira, IDeg and liraglutide with regard to the overall and nocturnal cumulative mean number of episodes per patient for DUAL I and ext using the ADA-documented symptomatic hypoglycaemia definition were, however, similar to those previously published with the original definitions,[7] albeit that the number of episodes per PYE were higher with the ADA definition. A similar pattern was seen for the profiles of cumulative mean number of episodes per patient for IDegLira and IGlar U100 for ADA-documented symptomatic episodes in comparison to those previously published for confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia.[3] The profiles of the cumulative mean number of episodes continued to diverge throughout the trial , indicating that the difference was not just an effect of the titration phase; rather, the benefit appeared to be maintained or even increase with time over the course of the trial.

The comparisons of confirmed hypoglycaemia and ADA-documented symptomatic hypoglycaemia according to the baseline characteristics indicated consistency in the treatment difference between IDegLira and IDeg, liraglutide or IGlar U100, for either hypoglycaemia definition, across the age, sex and BMI categories. Overall, the outcomes according to age, sex and BMI further highlight the benefits of treatment with IDegLira across a variety of populations of patients with type 2 diabetes.[7,12]

A limitation of this study is that patients were not randomised according to dosing time. A further consideration is that hypoglycaemia data from randomized controlled trials are not necessarily indicative of real-world hypoglycaemia rates, which tend to be higher.[13] This may mean that the benefits of lower hypoglycaemia rates with IDegLira treatment, versus IDeg and IGlar U100, could be even greater in a clinical setting. However, this remains to be demonstrated, since in practice patients may not be titrated to such tight targets as in the trial setting. Another limitation of this study is that the analyses were not adjusted for multiplicity.

In conclusion, treatment with IDegLira, in comparison with IDeg and IGlar U100, results in lower rates of hypoglycaemia regardless of dosing time and definition of hypoglycaemia used. This effect is observed despite lower HbA_{1c} levels being achieved with IDegLira compared with IDeg and IGlar U100. Furthermore, the baseline characteristics of sex and BMI did not have a significant effect on the rate ratios across different hypoglycaemia definitions. Patients older than 65 years had a greater reduction in hypoglycaemia than patients younger than 65 years. Therefore, a broad variety of patients with type 2 diabetes might expect to reach their treatment targets with low hypoglycaemia rates during treatment with IDegLira.

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Author contributions

PN, EJ, IL, LL, and HJ made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; EJ, IL, LL, and HJ participated in drafting the article or revising it critically for important intellectual content; and PN, RC, EJ, IL,HJ, LL and SH gave final approval of the version to be submitted and any revised version.

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Conflicts of interest

PN received research funding from Novo Nordisk and works with Eli Lilly, Sanofi, AstraZeneca and other companies. RC has appeared on speakers' bureau or advisory boards for Novo Nordisk, Merck Sharp & Dohme, AstraZeneca, Eli Lilly & Co, Boehringer Ingelheim, Amgen and Sanofi Aventis. EJ has appeared on speakers' bureau or advisory boards for Novo Nordisk, Eli Lilly, AstraZeneca, Boehringer Ingelheim, MSD, Janssen, Roche and Novartis. IL received non-financial support from Novo Nordisk, Sanofi, AstraZeneca and Boehringer Ingelheim. HJ is an employee and shareholder of Novo Nordisk. LL is an employee and shareholder of Novo Nordisk. SH has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Eli Lilly & Co, Novo Nordisk, Takeda, Merck Sharp & Dohme and Becton Dickinson. He has also served as a speaker for which he received remuneration from AstraZeneca, Eli Lilly & Co, Novo Nordisk, Boehringer Ingelheim and Takeda and has received research support from Medtronic UK Ltd.

References

1. Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes Metab* 2012;14:944–950.

2. Gough SC, Bode B, Woo V et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes. *Lancet Diabetes Endocrinol* 2014;2:885–893.

3. Lingvay I, Pérez Manghi F, García-Hernández P et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. *JAMA* 2016;315:898–907.

4. Workgroup on Hypoglycemia, American Diabetes Association. Defining and Reporting Hypoglycemia in Diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005;28:1245–9.

5. Swinnen SG, Mullins P, Miller M, Hoekstra JB, Holleman F. Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. *Diabetologia* 2009;52:38–41.

6. The International Hypoglycaemia Study Group. Glucose concentrations of less thatn 3.0 mmol/L (54mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2016; 60:3–6

7. Gough SC, Bode BW, Woo VC et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. *Diabetes Obes Metab* 2015;17:965–973.

8. Sorli C, Harris S, Jodar E et al. IDeglira is efficacious across baseline HbA_{1c} categories in subjects with type 2 diabetes uncontrolled on SU, GLP-1RA or insulin glargine: analyses from completed phase 3b trials. *Diabetes* 2016;65(Suppl 1):A238, 925-P

9. Farngren J, Persson M, Ahrén B. Effect of the GLP-1 Receptor Agonist Lixisenatide on Counterregulatory Responses to Hypoglycemia in Subjects With Insulin- Treated Type 2 Diabetes. *Diabetes Care* 2016;39(2):242–249.

10. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamics variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab*. 2016;14(9):859-64

11. Heller S, Mathieu C, Kapur R, Wolden ML, Zinman B. A meta-analysis of rate ratios for nocturnal confirmed hypoglycemia with insulin degludec vs. insulin glargine using different definitions for hypoglycemia. *Diabetic Medicine* 2016;33:478–487.

12. Rodbard HW, Buse JB, Woo V et al. Benefits of combination of insulin degludec and liraglutide are independent of baseline glycated haemoglobin level and duration of type 2 diabetes. *Diabetes Obes Metab* 2016;18:40–8.

13. Elliott L, Fidler C, Ditchfield A, Stissing T. Hypoglycemia Event Rates: A Comparison Between Real-World Data and Randomized Controlled Trial Populations in Insulin-Treated Diabetes. *Diabetes Ther* 2016;7:45–60.

Legends to figures:

Figure 1. Estimated rate ratio of hypoglycaemia by hypoglycaemia definition for (A) IDegLira vs. IDeg and (B) IDegLira vs. liraglutide for DUAL I ext and (C) IDegLira vs. IGlar U100 for DUAL V.

Figure 2. Cumulative mean number of ADA-documented symptomatic hypoglycaemic episodes per patient for (A) IDegLira, IDeg and liraglutide for DUAL I and DUAL I ext and (B) IDegLira and IGlar U100 in DUAL V.

Figure 3. Estimated rate ratio of hypoglycaemia (based on original definition) by dosing time for (A) IDegLira vs. IDeg and (B) IDegLira vs. liraglutide for DUAL I and DUAL I ext and (C) IDegLira vs. IGlar U100 for DUAL V.

Figures and Tables

Table 1. Description of different hypoglycaemia definitions used in analyses.

	Analysis	Description
Definition of hypoglycaemia	Confirmed hypoglycaemia (original)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat
	Overall confirmed symptomatic hypoglycaemia	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat, accompanied by reported symptoms
	ADA-documented symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose ≤3.9 mmol/L (≤70 mg/dL)
Timescales for nocturnal period	Nocturnal confirmed hypoglycaemia (00:01–05:59)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat occurring between 00:01 and 05:59 h [both inclusive]
	Nocturnal confirmed symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat, occurring between 00:01 and 05:59 h [both inclusive]
	Nocturnal ADA-documented symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose ≤3.9 mmol/L (≤70 mg/dL) occurring between 00:01 and 05:59 h [both inclusive]
	Nocturnal confirmed hypoglycaemia (21:59–05:59 h)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat occurring between 21:59 and 05:59 h [both inclusive]
	Nocturnal confirmed hypoglycaemia (00:01–07:59 h)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat occurring between 00:01 and 07:59 h [both inclusive]

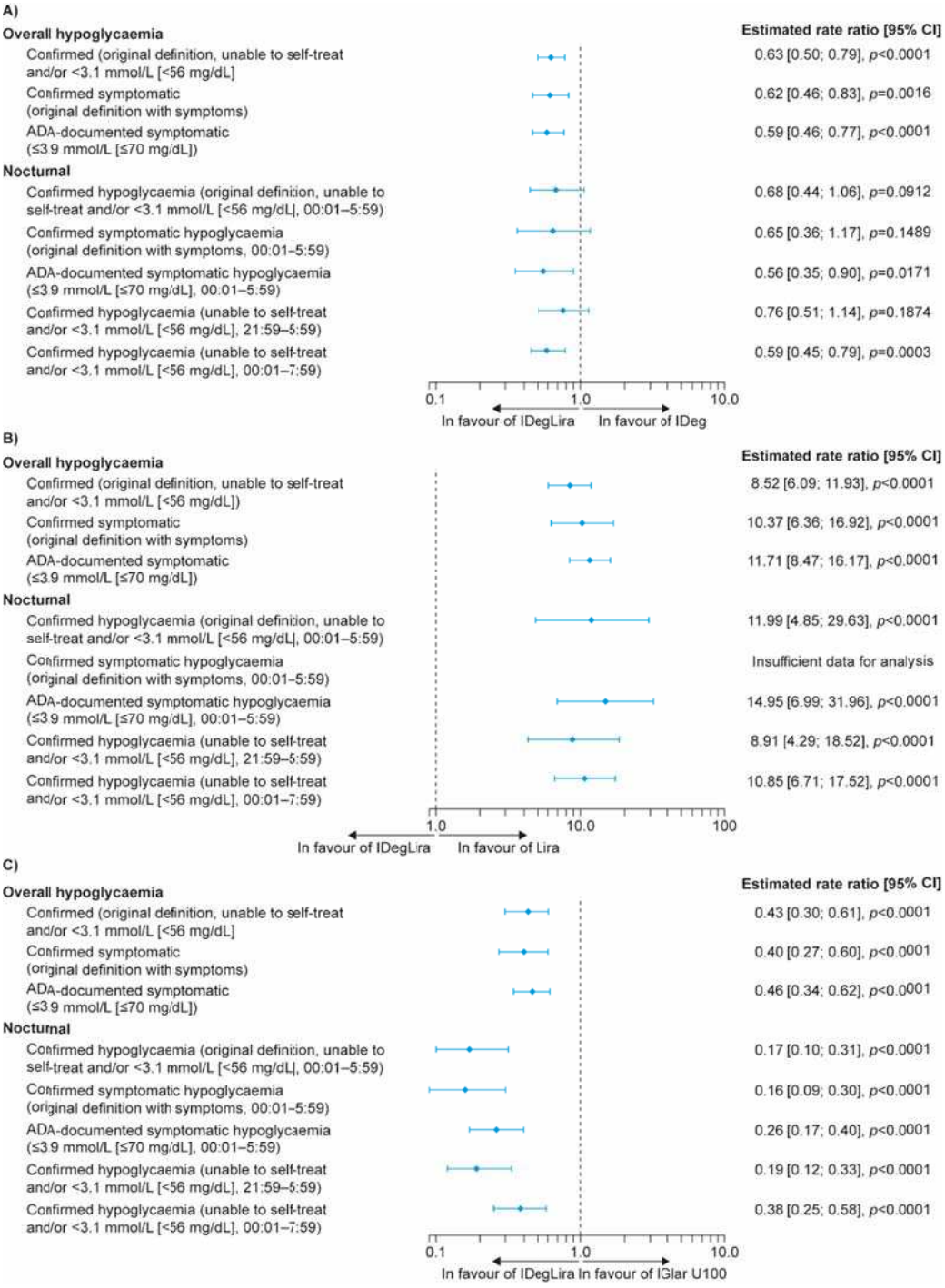
Table 2. Observed rates of hypoglycaemia.

	Episodes per PYE		
DUAL I:IDegLira (N=825), IDeg (N=412), liraglutide (N=412)	**IDegLira**	**IDeg**	**Liraglutide**
Confirmed hypoglycaemia (original)			
Main trial period	1.80	2.56	0.22
Trial extension period	1.77	2.79	0.19
Overall confirmed symptomatic hypoglycaemia			
Main trial period	0.67	1.08	0.06
Trial extension period	0.70	1.13	0.07
ADA-documented symptomatic hypoglycaemia			
Main trial period	4.12	5.74	0.35
Trial extension period	4.20	6.40	0.37
Nocturnal confirmed hypoglycaemia (00:01–05:59 h)			
Main trial period	0.22	0.28	0.03
Trial extension period	0.22	0.37	0.02
Nocturnal confirmed symptomatic hypoglycaemia			
Main trial period	0.08	0.10	NA
Trial extension period	0.09	0.14	NA
Nocturnal ADA-documented symptomatic hypoglycaemia			
Main trial period	0.54	0.66	0.05
Trial extension period	0.52	0.83	0.03
Nocturnal confirmed hypoglycaemia (21:59–05:59 h)			
Main trial period	0.24	0.26	0.02
Trial extension period	0.25	0.32	0.03
Nocturnal confirmed hypoglycaemia (00:01–07:59 h)			
Main trial period	0.76	1.15	0.09
Trial extension period	0.78	1.31	0.07

DUAL V: IDegLira (N=278), insulin glargine U100 (N=279)	**IDegLira**	**IGlar U100**
Confirmed hypoglycaemia (original)	2.23	5.05
Overall confirmed symptomatic hypoglycaemia	1.56	3.75
ADA documented symptomatic hypoglycaemia	8.03	15.63
Nocturnal confirmed hypoglycaemia (00:01–05:59 h)	0.22	1.23
Nocturnal confirmed symptomatic hypoglycaemia	0.16	1.02
Nocturnal ADA documented symptomatic hypoglycaemia	0.72	2.75
Nocturnal confirmed hypoglycaemia (21:59–05:59 h)	0.27	1.35
Nocturnal confirmed hypoglycaemia (00:01–07:59)	1.17	2.94

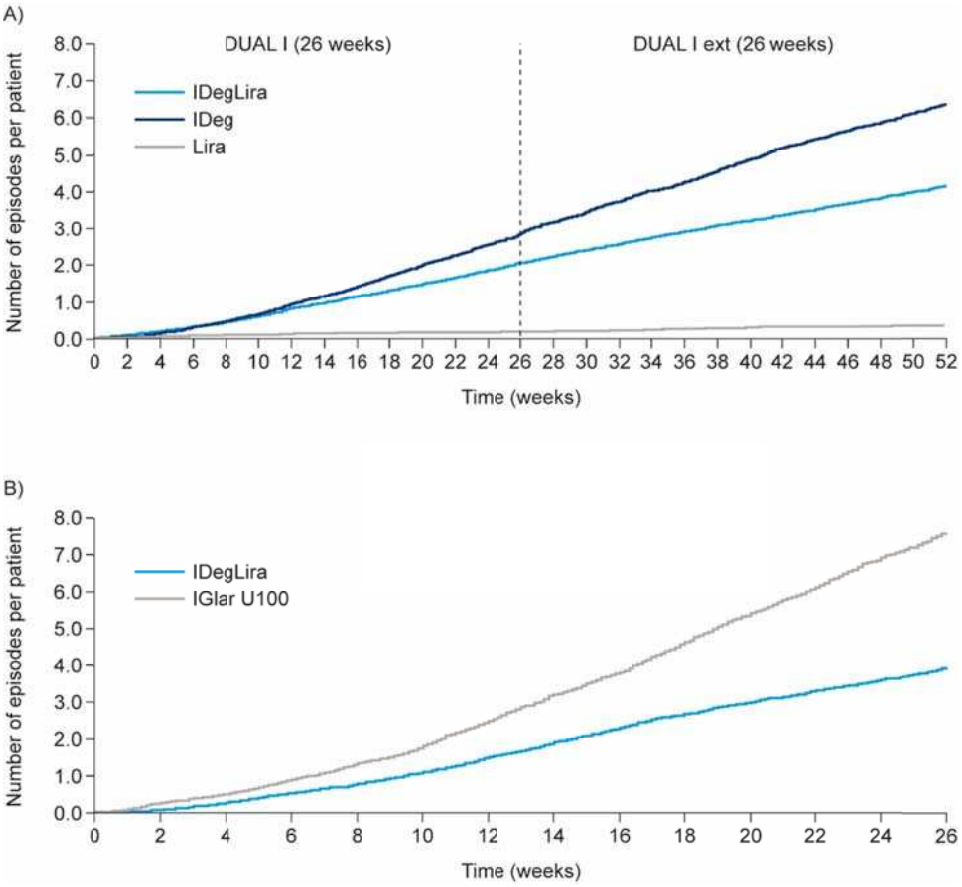
Data based on the safety analysis set. ADA, American Diabetes Association; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; PYE, patient-year of exposure; NA, not applicable.

Figure 1. Estimated rate ratio of hypoglycaemia by hypoglycaemia definition for (A) IDegLira vs IDeg and (B) IDegLira vs liraglutide for DUAL I ext and (C) IDegLira vs IGlar U100 for DUAL V.



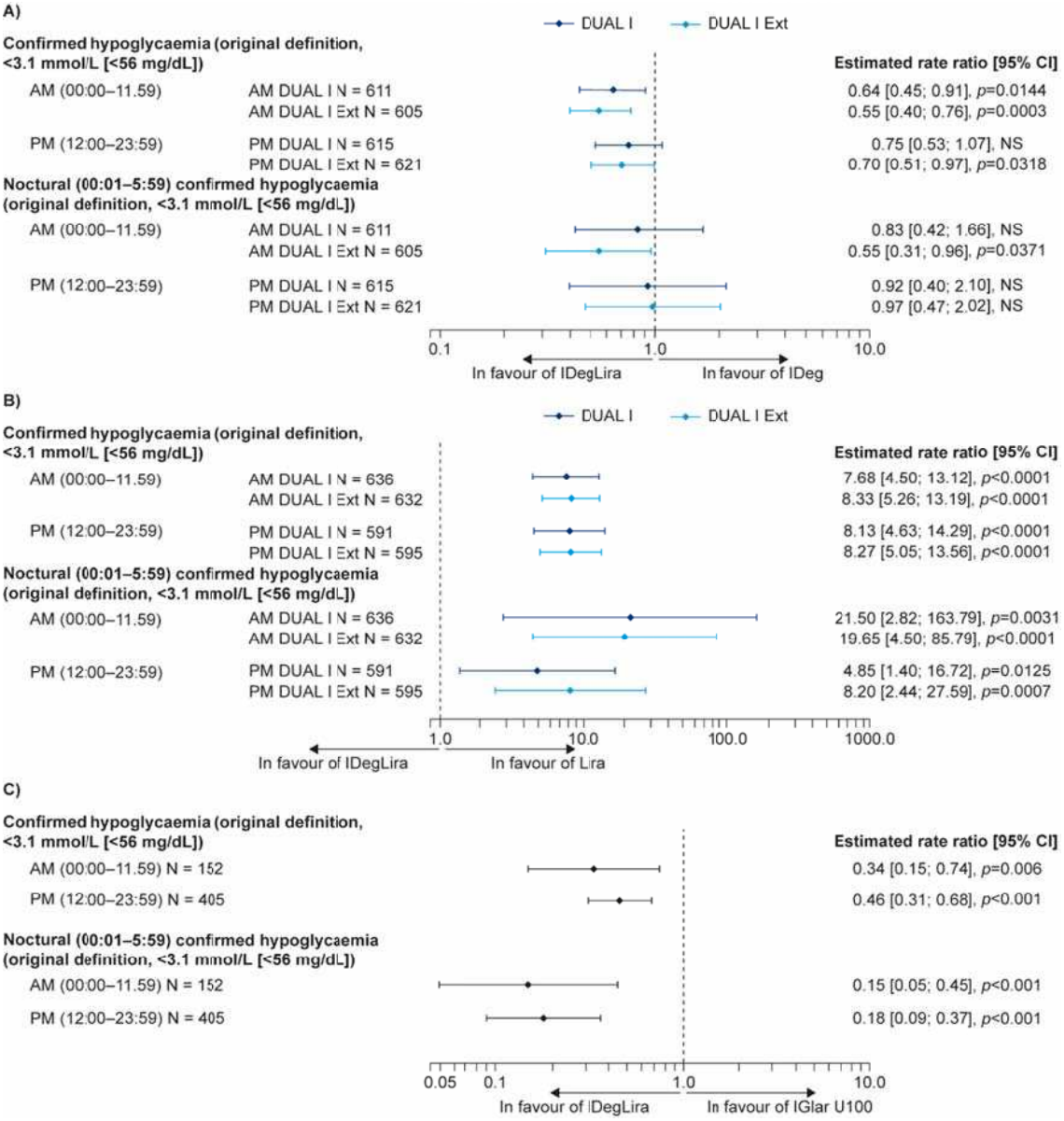
Data based on the full analysis set. The number of hypoglycaemic events was analysed using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, country/region and relevant stratification factors (in DUAL I ext only) of previous OAD treatment, baseline HbA_{1c} stratum, and substudy participation as fixed effects. ADA, American Diabetes Association; CI, confidence interval; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug

Figure 2. Cumulative mean number of ADA-documented symptomatic hypoglycaemic episodes per patient for (A) IDegLira, IDeg and liraglutide for DUAL I and DUAL I ext and (B) IDegLira and IGlar U100 in DUAL V.



Data based on the safety analysis set. ADA-documented symptomatic hypoglycaemic episode defined as typical symptoms of hypoglycaemia confirmed by a plasma glucose ≤3.9 mmol/L (≤70 mg/dL). ADA, American Diabetes Association; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; Lira, liraglutide.

Figure 3. Estimated rate ratio of hypoglycaemia (based on original definition) by dosing time for (A) IDegLira vs IDeg and (B) IDegLira vs liraglutide for DUAL I and DUAL I ext and (C) IDegLira vs IGlar U100 for DUAL V .



Data based on the full analysis set. The number of hypoglycaemic events was analysed using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, country/region and relevant stratification factors (in DUAL I/ext only) of previous OAD treatment, baseline HbA_{1c} stratum, and substudy participation as fixed effects. CI, confidence interval; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; Lira, liraglutide; OAD, oral antidiabetic drug.